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(21) International Application Number: PCT/US96/17991 (22) International Filing Date: 4 November 1996 (04.11.96) (30) Priority Data: 08/553,008 3 November 1995 (03.11.95) US (71) Applicant: EDWARD MENDELL CO., INC. [US/US]; 2981 Route 22, Patterson, NY 12563 (US). (72) Inventors: BAICHWAL, Anand, R.; 5 Kendell Drive, Wappinger Falls, NY 12590 (US). McCALL, Troy, W.; 4 Sullivan Farm, New Milford, CT 06776 (US). (74) Agents: RASKIN, Martin, G. et al.; Steinberg, Raskin & Davidson, P.C., 1140 Avenue of the Americas, New York, NY 10036 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: CONTROLLED RELEASE FORMULATION (ALBUTEROL) (57) Abstract A sustained release pharmaceutical formulation and methods of making and using the same are provided. The sustained release pharmaceutical formulation includes a sustained release excipient including a gelling agent, an inert pharmaceutical diluent, an optional hydrophobic material and/or hydrophobic coating, and a medicament for sustained oral administration.		

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CONTROLLED RELEASE FORMULATION (ALBUTEROL)FIELD OF THE INVENTION

10 The present invention relates to controlled
release formulations which may be blended with a wide
range of therapeutically active medicaments and made
into controlled release solid dosage forms for oral
administration.

15

BACKGROUND OF THE INVENTION

 The advantages of controlled release products are
well known in the pharmaceutical field and include the
ability to maintain a desired blood level of a
20 medicament over a comparatively longer period of time
while increasing patient compliance by reducing the
number administrations. These advantages have been
attained by a wide variety of methods. For example,
different hydrogels have been described for use in
25 controlled release medicines, some of which are
synthetic, but most of which are semi-synthetic or of
natural origin. A few contain both synthetic and
non-synthetic material. However, some of the systems
require special process and production equipment, and
30 in addition some of these systems are susceptible to
variable drug release.

 Oral controlled release delivery systems should
ideally be adaptable so that release rates and profiles
can be matched to physiological and chronotherapeutic
35 requirements. In U.S. Patent Nos. 4,994,276,
5,128,143, and 5,135,757, hereby incorporated by

5 reference in their entireties, it is reported that a
controlled release excipient which is comprised of a
synergistic combination of heterodisperse
polysaccharides (e.g., a heteropolysaccharide such as
xanthan gum in combination with a polysaccharide gum
10 capable of cross-linking with the heteropolysaccharide,
such as locust bean gum, in an aqueous environment) is
capable of being processed into oral solid dosage forms
using either direct compression (i.e., dry
granulation), following addition of drug and lubricant
15 powder, conventional wet granulation, or a combination
of the two. The release of the medicament from the
formulations therein proceeded according to zero-order
or first-order mechanisms.

The controlled release excipients disclosed in
20 U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757
are commercially available under the trade name TIMERx®
from Edward Mendell Co., Inc., Patterson, N.Y., which
is the assignee of the present invention.

European Pat. No. 234670 B describes a controlled-
25 release pharmaceutical formulation containing xanthan
gum wherein the xanthan gum comprises from about 7.5 to
about 28 percent, by weight, of the formulation except
for a formulation wherein the controlled release
carrier comprises a mixture of 15-50 parts by weight
30 dimethylsiloxane, 30-100 parts by weight silicic acid,
30-100 parts by weight mannans or galactans or a
mixture thereof, 50-150 parts by weight xanthans and 5-
75 parts by weight micronized seaweed.

However, heretofore there has been no teaching of
35 a controlled release formulation providing a novel and
unexpected combination of suitable proportions of a
homopolysaccharide such as, e.g., xanthan gum, a

5 heteropolysaccharide, such as, e.g., locust bean gum,
together with an inert diluent and a pharmacologically
acceptable hydrophobic material, so as to provide an
improvement in controlled release properties for such
an active medicament.

10

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of the present
invention to provide a controlled release formulation
for a therapeutically active medicament.

15

It is a further object of the present invention to
provide a method for preparing a controlled release
formulation for a therapeutically active medicament.

20

It is yet another object of the present invention
to provide a controlled release excipient which may be
used in the preparation of a sustained release oral
solid dosage form of a therapeutically active
medicament that provides an even rate of release of an
active medicament.

25

It is a further object of the present invention to
provide a controlled release excipient which, when
combined with an effective amount of a bronchodilator,
such as albuterol, is suitable for providing a
sustained release of that medicament so as to provide a
therapeutically effective blood level of the medicament
for e.g., 12 or 24 hours, without allowing an excessive
early release of medication, and where the release
kinetics are unaffected by the contents of the
patient's gastrointestinal tract.

30

It is yet a further object of the present
invention to provide a method for treating patients
with an active medication in controlled release form.

35

The above-mentioned objects and others are

5 achieved by virtue of the present invention, which
relates in-part to a controlled release formulation
comprising a therapeutically effective amount of a
medicament, and a controlled release excipient
comprising a gelling agent and a swelling agent, such
10 as, for example, a homopolysaccharide, a
heteropolysaccharide, an inert diluent.

In certain preferred embodiments of the invention,
the ratio of the heteropolysaccharide gum to the
homopolysaccharide gum is from about 1:3 to about 3:1.
15 More preferably, the ratio is about 1:1. Preferably,
the heteropolysaccharide gum includes xanthan gum and
the homopolysaccharide gum includes locust bean gum.

The present invention is also related to a
sustained release oral solid dosage form for albuterol
or salts or derivatives thereof in an amount necessary
20 to render a therapeutic effect in a human patient. The
albuterol is present in an amount ranging from, e.g.,
about 2 through about 50% by weight of the total
formulation, or preferably from about 1 through about
25 10% by weight or more preferably from about 1 through
about 6% by weight of the total formulation.

The dosage form includes an inert pharmaceutical
diluent so that the ratio of the inert diluent to the
gelling agent is from about 1:8 to about 8:1.
30 Preferably, the diluent is from the group consisting of
a pharmaceutically acceptable saccharide, polyhydric
alcohol, a pre-manufactured direct compression diluent,
and mixtures of any of the foregoing. The diluent can
also be a saccharide such as sucrose, dextrose,
35 lactose, microcrystalline cellulose, fructose, xylitol,
sorbitol, a starch, and mixtures thereof.

5 The dosage form optionally includes a
pharmaceutically acceptable hydrophobic material. Any
pharmaceutically acceptable hydrophobic material may be
suitably employed. Suitable hydrophobic materials
include carboxymethylcellulose, cellulose acetate
10 phthalate, polyvinyl acetate phthalate, hydroxypropyl-
methylcellulose phthalate, ethylcellulose, a copolymer
of acrylic and methacrylic and esters, waxes, shellac,
zein, hydrogenated vegetable oils, and mixtures of any
of the foregoing. Preferably, the hydrophobic material
15 selected from cellulose ether, a cellulose ester and an
alkylcellulose, such as ethylcellulose and
carboxymethylcellulose. The hydrophobic material may
be included in the dosage form in an amount effective
to slow the hydration of the gelling agent when exposed
20 to an environmental fluid.

 The hydrophobic material is preferably present in
an amount ranging from about 1 through about 90%, by
weight, of the solid dosage form, and can also be
present in an amount ranging from about 25% through
25 about 50%, by weight, of the solid dosage form.

 The medicament can be any medicament for which an
orally administered controlled release form is desired.
Preferably, the formulation is prepared to include a
pharmaceutically effective amount of albuterol or a
30 salt or derivative thereof.

 The controlled release solid dosage form can be
prepared in any conventional orally administered dosage
form, including a tablet, as a granular form and as a
granular form administered in a gelatin capsule
35 containing a sufficient amount of the granules to
provide an effective dose of the included
therapeutically active medicament. For a tablet dosage

5 form, at least part of a surface of the tablet can
optionally be coated with a hydrophobic material to a
weight gain from about 1 to about 20 percent, by
weight. Further, a granular dosage form can optionally
10 be coated with a hydrophobic coating material to a
weight gain that ranges from about 1% to about 20%.
The hydrophobic material can be selected from, e.g., a
cellulose ether, a cellulose ester and an
alkylcellulose. The hydrophobic material can
optionally be applied before, during or after the
15 process of tableting. In addition, if there is a need
for an early release of the active medicament, the
coating can optionally be formulated to include from
about 10 to about 40 percent of the total amount of the
active medicament in a quick release external layer.

20 The invention also relates to methods for
preparing a controlled release solid dosage form as
described above for providing an active medicament in
an amount effective for treating a patient for from 12
to about 24 hours. The method includes the steps of
25 preparing a sustained release excipient comprising from
about 10 to about 99 percent by weight of a gelling
agent comprising a heteropolysaccharide gum and a
homopolysaccharide gum capable of cross-linking said
heteropolysaccharide gum when exposed to an
30 environmental fluid, the ratio of said
heteropolysaccharide gum to said homopolysaccharide gum
being from about 1:3 to about 3:1, and from about 0 to
about 89 percent by weight of an inert pharmaceutical
diluent, and optionally from about 1 to 90% by weight
35 of a pharmaceutically acceptable hydrophobic material;
and adding an effective amount of a medicament to
provide a final product having a ratio of medicament to

5 gelling agent from about 1:3 to about 1:8, so that a gel matrix is created.

The medicament to be added is preferably albuterol or salts or derivatives thereof in an amount ranging from, e.g., about 2 to about 50% by weight of the total
10 formulation, or preferably from about 1 to about 10% by weight or more preferably from about 1 to about 6% by weight of the total formulation.

The resulting mixture of the sustained release
15 excipient preferably includes from about 10 to about 75 percent gelling agent, from about 0 to about 90% hydrophobic material and from about 30 to about 75 percent inert diluent. Thereafter, the dosage form can be tableted, granulated with a pharmaceutically
20 acceptable hydrophobic material or placed in gelatine capsules. Optionally the tablet can be coated with a hydrophobic coating to a weight gain from about 1% to about 20%.

Preferably, the medicament is albuterol or a salt
25 or derivative thereof in an amount effective to provide therapeutically effective blood levels of said medicament for at least 24 hours.

The present invention is further related to a method of treating a patient comprising orally
30 administering the sustained release albuterol tablets to a patient, thereby providing therapeutically effective blood levels of the medicament for at least about 24 hours.

By "sustained release" it is meant for purposes of
35 the present invention that the therapeutically active medicament is released from the formulation at a controlled rate such that therapeutically beneficial

5 blood levels (but below toxic levels) of the medicament
are maintained over an extended period of time, e.g.,
providing a 24 hour dosage form.

 The term "environmental fluid" is meant for pur-
poses of the present invention to encompass, e.g., an
10 aqueous solution, such as that used for in-vitro dis-
solution testing, or gastrointestinal fluid.

 In one aspect the invention provides formulations
having particular pharmacokinetic properties. Thus,
simply by way of example, the invention provides
15 formulations suitable for oral administration that,
when orally administered to a patient, provide a
medicament plasma concentration-time curve with an area
under the curve-calculated to infinity ("AUC."), ranging
from about 89 to about 150 (ng-hours/ml) or even from
20 about 112 to about 129 (ng-hours/ml). Further, the
formulations according to the invention can provide,
e.g., an AUC. ranging from about 57 to about 157 (ng-
hours/ml) (fasting patient) or from about 75 to about
162 (ng-hours/ml) (fed patient).

25 In addition, for example, mean peak plasma
concentrations (C_{max}) ranging from about 7 to about 12
ng/ml or even from about, 9.5 to about 12 ng/ml. are
provided. Further, the formulations according to the
invention can provide, e.g., a C_{max} ranging from about
30 4.5 to about 19 ng/ml (fasting patient) or from about 6
to about 16 ng/ml (fed patient).

 In another example, time to mean peak plasma
concentration (T_{max}) ranging from about 3 to about 10
hours or even from about 3.5 to about 8 hours are
35 provided. Further, the formulations according to the
invention can provide, e.g., a T_{max} ranging from about
3 to about 6 hours (fasting patient) or from about 3 to

5 about 8 hours (fed patient).

In a further example, the formulation according to the invention provides, for example, ratios of AUC₀₋₈ (fasting patient) to AUC₀₋₈ (fed patient) that range from about 0.50 to about 0.70.

10 Further still, the formulation provides, for example ranges of C_{max} (fasting patient) divided by C_{max} (fed patient) from about 0.90 to about 1.10.

BRIEF DESCRIPTION OF THE FIGURES

15 Figure 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type II dissolution with a pH change to simulate gastric passage and stirring at 50 rpm.

20 Figure 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) and conducted as a Type III dissolution with a pH change to simulate gastric passage and stirring at 15 rpm.

25 Figure 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in
30 fasted subject.

DETAILED DESCRIPTION

As reported in U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757, the disclosures of which are
35 hereby incorporated by reference herein in their entireties, the heterodisperse excipient comprises a

5 gelling agent of both hetero- and homo-polysaccharides
which exhibit synergism, e.g., the combination of two
or more polysaccharide gums produce a higher viscosity
and faster hydration than that which would be expected
10 by either of the gums alone, the resultant gel being
faster-forming and more rigid.

 In the present invention, it has been found that a
sustained release excipient comprising only the gelling
agent (heterodisperse polysaccharides, e.g., xanthan
gum and locust bean gum, may not be sufficient to
15 provide a suitable sustained release of an active
medicament to provide a 12 or 24 hour formulation, when
the formulation is exposed to a fluid in an environment
of use, e.g. an aqueous solution or gastrointestinal
fluid.

20 In certain embodiments, the present invention is
related to the surprising discovery that by granulating
the sustained release excipient with a solution or
dispersion of a pharmacologically acceptable
hydrophobic material prior to admixture of the
25 sustained release excipient with the medicament and
tableting, the medicament may provide therapeutically
effective blood levels for extended periods of time,
e.g., from about 12 to about 24 hours. The hydrophobic
material is present in a range from about 0 to about
30 90%, by weight, of the sustained release excipient and
in a preferred embodiment, is present in a range from
about 1 to 20 percent of the sustained release
excipient or from about 25 to about 75 percent of the
sustained release excipient.

35 The sustained release excipient can be granulated
with a pharmacologically acceptable hydrophobic
material such as, for, example, an alkylcellulose, a

5 cellulose ether, a cellulose ester. In particular, the hydrophobic material can be alkylcellulose such as carboxymethylcellulose ("CMC"), cellulose acetate phthalate ("CAP"), hydroxypropylmethylcellulose phthalate ("HPMCP") or a polyvinyl acetate polymer such
10 as polyvinyl acetate phthalate ("PVAP").

In certain preferred embodiments of the present invention, the sustained release excipient is prepared by mixing the gelling agent and an inert diluent. The gelling agent preferably ranges, e.g., from about 10 to
15 about 75 percent of the sustained release excipient. Thereafter, the mixture is granulated with a solution or dispersion of a hydrophobic material in an amount effective to slow the hydration of the gelling agent without disrupting the hydrophilic matrix. Next, the
20 medicament is added, and the resultant mixture is tableted.

In other preferred embodiments of the present invention, the tablets prepared as set forth above are then coated with a hydrophobic material to a weight
25 gain from about 1 to about 20 percent by weight. The hydrophobic material can be an alkylcellulose such as, for example, an aqueous dispersion of ethylcellulose (commercially available, for example, as Aquacoat®, available from FMC or Surelease®, available from
30 Colorcon).

The term "heteropolysaccharide" as used in the present invention is defined as a water-soluble polysaccharide containing two or more kinds of sugar
units, the heteropolysaccharide having a branched or
35 helical configuration, and having excellent water-wicking properties and immense thickening properties.

An especially preferred heteropolysaccharide is

5 xanthan gum, which is a high molecular weight ($>10^6$)
heteropolysaccharide. Other preferred
heteropolysaccharides include derivatives of xanthan
gum, such as deacylated xanthan gum, the carboxymethyl
ether, and the propylene glycol ester.

10 The homopolysaccharide gums used in the present
invention which are capable of cross-linking with the
heteropolysaccharide include the galactomannans, i.e.,
polysaccharides which are composed solely of mannose
and galactose. Galactomannans which have higher
15 proportions of unsubstituted mannose regions have been
found to achieve more interaction with the
heteropolysaccharide. Locust bean gum, which has a
higher ratio of mannose to galactose, is especially
preferred as compared to other galactomannans such as
20 guar and hydroxypropyl guar.

 The controlled release properties of the
formulations of the present invention may be optimized
when the ratio of heteropolysaccharide gum to
homopolysaccharide material is about 1:1, although
25 heteropolysaccharide gum in an amount of from about 20
to about 80 percent or more by weight of the
heterodisperse polysaccharide material provides an
acceptable slow release product. The combination of
any homopolysaccharide gums known to produce a
30 synergistic effect when exposed to aqueous solutions
may be used in accordance with the present invention.
It is also possible that the type of synergism which is
present with regard to the gum combination of the
present invention could also occur between two
35 homogeneous or two heteropolysaccharides. Other
acceptable gelling agents which may be used in the
present invention include those gelling agents well-

5 known in the art. Examples include vegetable gums such
as alginates, carrageenan, pectin, guar gum, xanthan
gum, modified starch, hydroxypropylmethylcellulose,
methylcellulose, and other cellulosic materials such as
10 sodium carboxymethylcellulose and
hydroxypropylcellulose. This list is not meant to be
exclusive.

The combination of xanthan gum with locust bean
gum with or without the other homopolysaccharide gums
is an especially preferred gelling agent. The
15 chemistry of certain of the ingredients comprising the
excipients of the present invention such as xanthan gum
is such that the excipients are considered to be self-
buffering agents which are substantially insensitive to
the solubility of the medicament and likewise
20 insensitive to the pH changes along the length of the
gastrointestinal tract.

The inert pharmaceutical diluent (i.e., filler) of
the sustained release excipient preferably comprises a
pharmaceutically acceptable saccharide, including a
25 monosaccharide, a disaccharide, or a polyhydric
alcohol, a pre-manufactured direct compression diluent,
and/or mixtures of any of the foregoing. Examples of
suitable inert pharmaceutical fillers include sucrose,
dextrose, lactose, microcrystalline cellulose,
30 fructose, xylitol, sorbitol, a starch, mixtures thereof
and the like. However, it is preferred that a soluble
pharmaceutical filler such as lactose, dextrose,
sucrose, or mixtures thereof be used. If the mixture
is to be manufactured without a wet granulation step,
35 and the final product is to be tableted, it is
preferred that all or part of the inert diluent
comprise a pre-manufactured direct compression diluent.

5 Such direct compression diluents are widely used in the
pharmaceutical arts, and may be obtained from a wide
variety of commercial sources. Examples of such pre-
manufactured direct compression excipients include
Emcocel® (microcrystalline cellulose, N.F.), Emdex®
10 (dextrates, N.F.), and Tab-Fine® (a number of direct-
compression sugars including sucrose, fructose, and
dextrose), all of which are commercially available from
Edward Mendell Co., Inc., Patterson, New York). Other
direct compression diluents include Anhydrous lactose
15 (Lactose N.F., anhydrous direct tableting) from
Sheffield Chemical, Union, N.J. 07083; Elcems® G-250
(Powdered cellulose, N.F.) from Degussa, D-600
Frankfurt (Main) Germany; Maltrin® (Agglomerated
maltodextrin) from Grain Processing Corp., Muscatine,
20 IA 52761; Neosorb 60® (Sorbitol, N.F., direct-
compression) from Roquette Corp., 645 5th Ave., New
York, NY 10022; Nu-Tab® (Compressible sugar, N.F.) from
Ingredient Technology, Inc., Pennsauken, NJ 08110;
Polyplasdane XL® (Crospovidone, N.F., cross-linked
25 polyvinylpyrrolidone) from GAF Corp., New York, NY
10020; Primojel® (Sodium starch glycolate, N.F.,
carboxymethyl starch) from Generichem Corp., Little
Falls, NJ 07424; Solka Floc® (Cellulose floc) from
Edward Mendell Co., Carmel, NY 10512; Fast-Flo Lactose®
30 (Lactose N.F., spray dried) from Foremost Whey
Products, Baraboo, WI 53913 and DMV Corp., Vehgel,
Holland; and Sta-Rx 1500® (Starch 1500) (Pregelatinized
starch, N.F., compressible) from Colorcon, Inc., West
Point, PA 19486. However, it is preferred that a
35 soluble pharmaceutical filler such as lactose,
dextrose, sucrose, or mixtures thereof be used.

In certain embodiments of the present invention,

5 the sustained release excipient comprises from about 10
to about 99 percent by weight of a gelling agent
comprising a heteropolysaccharide gum and a
homopolysaccharide gum and from about 0 to about 89
percent by weight of an inert pharmaceutical diluent.
10 In other embodiments, the sustained release excipient
comprises from about 10 to about 75 percent gelling
agent, and from about 30 to about 75 percent inert
diluent. In yet other embodiments, the sustained
release excipient comprises from about 30 to about 75
15 percent gelling agent and from about 15 to about 65
percent inert diluent.

The sustained release excipient of the present
invention may be further modified by incorporation of a
hydrophobic material which slows the hydration of the
20 gums without disrupting the hydrophilic matrix. This
is accomplished in preferred embodiments of the present
invention by granulating the sustained release
excipient with the solution or dispersion of a
hydrophobic material prior to the incorporation of the
25 medicament. The hydrophobic material may be selected
from an alkylcellulose such as ethylcellulose such as
carboxymethyl-cellulose ("CMC"), other hydrophobic
cellulosic materials, acrylic and/or methacrylic ester
polymers, copolymers of acrylic and methacrylic esters,
30 zein, waxes, other hydrophobic cellulosic materials,
cellulose acetate phthalate ("CAP"),
hydroxypropylmethylcellulose phthalate ("HPMCP") or a
polyvinyl acetate polymer such as polyvinyl acetate
phthalate ("PVAP"), hydrogenated vegetable oils, and
35 any other pharmaceutically acceptable hydrophobic
material known to those skilled in the art. The amount
of hydrophobic material incorporated into the sustained

5 release excipient is that which is effective to slow
the hydration of the gums without disrupting the
hydrophilic matrix formed upon exposure to an
environmental fluid.

10 In certain preferred embodiments of the present
invention, the hydrophobic material is included in the
sustained release excipient in an amount from about 1
to about 20 percent by weight. The solvent for the
hydrophobic material may be an aqueous or organic
solvent, or mixtures thereof.

15 Examples of commercially available alkylcelluloses
are Aquacoat® (aqueous dispersion of ethylcellulose
available from FMC), Surelease® (aqueous dispersion of
ethylcellulose available from Colorcon). Examples of
commercially available acrylic polymers suitable for
20 use as the hydrophobic material include Eudragit® RS
and RL (copolymers of acrylic and methacrylic acid
esters having a low content (e.g., 1:20 or 1:40) of
quaternary ammonium compounds).

25 Once the sustained release excipient of the
present invention has been prepared, it is then
possible to blend the same with the medicament, e.g.,
in a high shear mixer. In one embodiment, the
formulation is prepared by dry blending the components,
e.g., a heteropolysaccharide, a homopolysaccharide, an
30 inert filler, and a hydrophobic material, optionally
followed by the addition of a suitable amount of water,
with continued blending, followed by dry granulation in
a fluid bed dryer and then milling of the resulting
granulation product.

35 A wide variety of therapeutically active agents
can be used in conjunction with the present invention.
The therapeutically active agents (e.g., pharmaceutical

5 agents) which may be used in the compositions of the
present invention include drugs ranging in solubility
from water soluble to water insoluble. Examples of
such therapeutically active agents include
antihistamines (e.g., dimenhydrinate, diphenhydramine,
10 chlorpheniramine and dexchlorpheniramine maleate),
analgesics (e.g., aspirin, codeine, morphine,
dihydromorphone, oxycodone, etc.), non-steroidal anti-
inflammatory agents (e.g., naproxyn, diclofenac,
indomethacin, ibuprofen, sulindac), anti-emetics (e.g.,
15 metoclopramide), anti-epileptics (e.g., phenytoin,
meprobamate and nitrazepam), vasodilators (e.g.,
nifedipine, papaverine, diltiazem and nicardirine),
anti-tussive agents and expectorants (e.g., codeine
phosphate), anti-asthmatics (e.g. theophylline),
20 antacids, anti-spasmodics (e.g. atropine, scopolamine),
antidiabetics (e.g., insulin), diuretics (e.g.,
ethacrynic acid, bendrofluazide), anti-hypotensives
(e.g., propranolol, clonidine), antihypertensives
(e.g., clonidine, methyldopa), bronchodilators (e.g.,
25 albuterol), steroids (e.g., hydrocortisone,
triamcinolone, prednisone), antibiotics (e.g.,
tetracycline), antihemorrhoidals, hypnotics,
psychotropics, antidiarrheals, mucolytics, sedatives,
decongestants, laxatives, vitamins, stimulants
30 (including appetite suppressants such as
phenylpropanolamine). The above list is not meant to
be exclusive.

In a preferred embodiment, the therapeutically
active agents are sympathomimetics such as, dobutamine
35 hydrochloride, dopamine hydrochloride, ephedrine
sulfate, epinephrine, fenfluramine hydrochloride,
isoetharine, isoproterenol, mephentermine sulfate,

5 metaproterenol sulfate, metaraminol bitartrate,
methoxamine hydrochloride, norepinephrine bitartrate,
phenylephrine hydrochloride, phenylpropanolamine
hydrochloride, pseudoephedrine, ritodrine
hydrochloride, terbutaline sulfate, tetrahydrozoline
10 hydrochloride, triprolidine and pseudoephedrine,
xylometazoline hydrochloride, isoproterenol and
dobutamine as well as beta2 selective adrenergic
agonists, including, for example, terbutaline,
albuterol, isoetharine, pirbuterol and bitolterol
15 (GOODMAN AND GILMAN's, THE PHARMACOLOGICAL BASIS OF
THERAPEUTICS, Eighth Edition, the disclosure of which
is incorporated herein by reference in its entirety).

Generally any flavoring or food additive such as
those described in Chemicals Used in Food Processing,
20 pub 1274 by the National Academy of Sciences, pages 63-
258, incorporated herein in its entirety, may be used.
Generally, the final product may include from about
0.1% to about 5% by weight flavorant.

The tablets of the present invention may also
25 contain effective amounts of coloring agents, (e.g.,
titanium dioxide, F.D. & C. and D. & C. dyes; see the
Kirk-Othmer Encyclopedia of Chemical Technology, Vol.
5, pp. 857-884, hereby incorporated by reference in its
entirety), stabilizers, binders, odor controlling
30 agents, and preservatives.

Alternatively, the inventive formulation can be
utilized in other applications wherein it is not
compressed. For example, the granulate can be admixed
with an active ingredient and the mixture then filled
35 into capsules. The granulate can further be molded
into shapes other than those typically associated with
tablets. For example, the granulate together with

5 active ingredient can be molded to "fit" into a particular area in an environment of use (e.g., an implant). All such uses would be contemplated by those skilled in the art and are deemed to be encompassed within the scope of the appended claims.

10 A hydrophobic material (e.g., a hydrophobic polymer) may be dissolved in an organic solvent or dispersed in an aqueous solution. Thereafter, the hydrophobic material may be used to coat the granulate of medicament/sustained release excipient. The
15 granulate may be coated with the hydrophobic coating to a weight gain of, e.g., from about 1 to about 20 percent, and preferably from about 5 to about 10 percent. The granulation is then preferably dried. Thereafter, the granulate may be further formulated
20 into an appropriate oral dosage form, for example, by compression of the resulting granulate into appropriately sized tablets, by filling gelatin capsules with an appropriate amount of the granulate (with or without compression of the granulate), as well
25 as use in the manufacture of other oral dosage forms known to those skilled in the art. This embodiment may be particularly beneficial to reduce the amount of drug released during the initial phases of dissolution when the formulation is exposed to fluid in an environment
30 of use, e.g., in vitro dissolution or in the gastrointestinal tract.

An effective amount of any generally accepted pharmaceutical lubricant, including the calcium or magnesium soaps may be added to the above-mentioned
35 ingredients of the excipient be added at the time the medicament is added, or in any event prior to compression into a said dosage form. An example of a

5 suitable lubricant is magnesium stearate in an amount of about 0.5 to about 3% by weight of the solid dosage form. An especially preferred lubricant is sodium stearyl fumarate, NF, commercially available under the trade name Pruv® from the Edward Mendell Co., Inc.

10 The sustained release excipients of the present invention have uniform packing characteristics over a range of different particle size distributions and are capable of processing into the final dosage form (e.g., tablets) using either direct compression, following
15 addition of drug and lubricant powder, or conventional wet granulation.

 The properties and characteristics of a specific excipient system prepared according to the present invention is dependent in part on the individual
20 characteristics of the homo and hetero polysaccharide constituents, in terms of polymer solubility, glass transition temperatures etc., as well as on the synergism both between different homo- and heteropolysaccharides and between the homo and
25 heteropolysaccharides and the inert saccharide constituent(s) in modifying dissolution fluid-excipient interactions.

 The combination of the gelling agent (i.e., a mixture of xanthan gum and locust beam gum) with the
30 inert diluent provides a ready-to-use product in which a formulator need only blend the desired active medicament and an optional lubricant with the excipient and then compress the mixture to form slow release tablets. The excipient may comprise a physical admix
35 of the gums along with a soluble excipient such as compressible sucrose, lactose or dextrose, although it is preferred to granulate or agglomerate the gums with

5 plain (i.e., crystalline) sucrose, lactose, dextrose,
etc., to form an excipient. The granulate form has
certain advantages including the fact that it can be
optimized for flow and compressibility; it can be
tableted, formulated in a capsule, extruded and
10 spheronized with an active medicament to form pellets,
etc.

The pharmaceutical excipients prepared in
accordance with the present invention may be prepared
according to any agglomeration technique to yield an
15 acceptable excipient product. In dry granulation
techniques, the excipients, i.e., the desired amounts
of the heteropolysaccharide gum, the homopolysaccharide
gum, and the inert diluent are mixed with an active
medicament and the mixture is then formed into tablets
20 and the like by compression, without the addition of
water or other solvent.

In wet granulation techniques, the desired amounts
of the heteropolysaccharide gum, the homopolysaccharide
gum, and the inert diluent are mixed together and
25 thereafter a moistening agent such as water, propylene
glycol, glycerol, alcohol or the like is added to
prepare a moistened mass. Next, the moistened mass is
dried. The dried mass is then milled with conventional
equipment into granules. Therefore, the excipient
30 product is ready to use.

The sustained release excipient is free-flowing
and directly compressible. Accordingly, the excipient
may be mixed in the desired proportion with a
therapeutically active medicament and optional
35 lubricant (dry granulation). Alternatively, all or
part of the excipient may be subjected to a wet
granulation with the active ingredient and thereafter

5 tableted. When the final product to be manufactured is
tablets, the complete mixture, in an amount sufficient
to make a uniform batch of tablets, is then subjected
to tableting in a conventional production scale
tableting machine at normal compression pressure, i.e.
10 about 2000-1600 lbs/sq in. However, the mixture should
not be compressed to such a degree that there is
subsequent difficulty in its hydration when exposed to
gastric fluid.

15 One of the limitations of direct compression as a
method of tablet manufacture is the size of the tablet.
If the amount of active (drug) is high, a
pharmaceutical formulator may choose to wet granulate
the active medicament with other excipients to attain a
more compact tablet. Usually the amount of
20 filler/binder or excipients needed in wet granulation
is less than that in direct compression since the
process of wet granulation contributes to some extent
toward the desired physical properties of a tablet.

25 The average tablet size for round tablets is
preferably about 300 mg to 750 mg and for capsule-
shaped tablets about 750 mg to 1000 mg.

30 The average particle size of the granulated
excipient of the present invention ranges from about 50
microns to about 400 microns and preferably from about
185 microns to about 265 microns. The particle size of
the granulation is not narrowly critical, the important
parameter being that the average particle size of the
granules, must permit the formation of a directly
compressible excipient which forms pharmaceutically
35 acceptable tablets. The desired tap and bulk densities
of the granulation of the present invention are
normally between from about 0.3 to about 0.8 g/ml, with

5 an average density of from about 0.5 to about 0.7 g/ml.
For best results, the tablets formed from the
granulations of the present invention are from about 6
to about 8 kg hardness. The average flow of the
10 granulations prepared in accordance with the present
invention are from about 25 to about 40 g/sec. Tablets
compacted using an instrumented rotary tablet machine
have been found to possess strength profiles which are
largely independent of the inert saccharide component.
15 Scanning electron photomicrographs of largely tablet
surfaces have provided qualitative evidence of
extensive plastic deformation on compaction, both at
the tablet surface and across the fracture surface, and
also show evidence of surface pores through which
initial solvent ingress and solution egress may occur.

20 In certain embodiments of the invention, the
tablet is coated with a sufficient amount of a
hydrophobic material, such as, e.g., a hydrophobic
polymer, to render the formulation capable of providing
a release of the medicament such that a 12 or 24 hour
25 formulation is obtained. The hydrophobic material
included in the tablet coating may be the same or
different material as compared to the hydrophobic
material which is optionally granulated with the
sustained release excipient.

30 In other embodiments of the present invention, the
tablet coating may comprise an enteric coating material
in addition to or instead of the hydrophobic coating.
Examples of suitable enteric polymers include cellulose
acetate phthalate, hydroxypropylmethylcellulose
35 phthalate, polyvinylacetate phthalate, methacrylic acid
copolymer, shellac, hydroxypropylmethylcellulose
succinate, cellulose acetate trimellitate, and mixtures

5 of any of the foregoing. An example of a suitable commercially available enteric material is available under the trade name Eudragit™ L 100-555.

10 In further embodiments, the dosage form may be a coating with a hydrophilic coating in addition to or instead of the above-mentioned coatings. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pennsylvania).

15 The coatings may be applied in any pharmaceutically acceptable manner known to those skilled in the art. For example, in one embodiment, the coating is applied via a fluidized bed or in a coating pan. For example, the coated tablets may be dried, e.g., at about 60-70°C for about 3-4 hours in a coating pan. The solvent for the hydrophobic material or enteric coating may be organic, aqueous, or a mixture of an organic and an aqueous solvent. The organic solvents may be, e.g., isopropyl alcohol, ethanol, and the like, with or without water.

25 In additional embodiments of the present invention, a support platform is applied to the tablets manufactured in accordance with the present invention. Suitable support platforms are well known to those skilled in the art. An example of suitable support platforms is set forth, e.g., in U.S. Patent No. 30 4,839,177, hereby incorporated by reference herein in its entirety. In that patent, the support platform partially coats the tablet, and consists of a polymeric material insoluble in aqueous liquids. The support platform may, for example, be designed to maintain its impermeability characteristics during the transfer of 35

5 the therapeutically active medicament. The support platform may be applied to the tablets, e.g., via compression coating onto part of the tablet surface, by spray coating the polymeric materials comprising the support platform onto all or part of the tablet surface, or by immersing the tablets in a solution of
10 the hydrophobic materials.

The support platform may have a thickness of, e.g., about 2 mm if applied by compression, and about 10 μ if applied via spray-coating or immersion-coating.
15 Generally, in embodiments of the invention wherein a hydrophobic material or enteric coating is applied to the tablets, the tablets are coated to a weight gain from about 1 to about 20%, and in certain embodiments preferably from about 5% to about 10%.

20 Materials useful in the hydrophobic coatings and support platforms of the present invention include derivatives of acrylic acid (such as esters of acrylic acid, methacrylic acid, and copolymers thereof) celluloses and derivatives thereof (such as
25 ethylcellulose), polyvinylalcohols, and the like.

In certain embodiments of the present invention, the tablet core includes an additional dose of the medicament included in either the hydrophobic or enteric coating, or in an additional overcoating coated
30 on the outer surface of the tablet core (without the hydrophobic or enteric coating) or as a second coating layer coated on the surface of the base coating comprising the hydrophobic or enteric coating material. This may be desired when, for example, a loading dose
35 of a therapeutically active agent is needed to provide therapeutically effective blood levels of the active agent when the formulation is first exposed to gastric

5 fluid. The loading dose of medicament included in the coating layer may be, e.g., from about 10% to about 40% of the total amount of medicament included in the formulation.

10 Albuterol Controlled Release Formulation

In a more preferred embodiment, the therapeutically active agent is albuterol, or salts or derivatives thereof (e.g., albuterol sulfate). Albuterol sulfate is a beta2 - selective adrenergic
15 agonist and is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease. Patient compliance and evenly maintained blood levels of the active drug are important for achieving good control of the symptoms of bronchospasm in such
20 patients. The half-life of albuterol sulfate in the human body is only about 5 hours. Thus, a controlled release form for the sustained delivery of albuterol provides improved patient compliance by reducing the number of doses per day and also provides more
25 consistent blood levels of albuterol for patients in need of such treatment.

The albuterol controlled release formulation is composed of synergistic heterodisperse polysaccharides together with a saccharide component. The synergism
30 between the homo- and hetero-polysaccharide components enables the manipulation of different rate controlling mechanisms. In order to achieve appropriate drug release, the saccharides were optimized based upon the magnitude of interactions and the ratio of one
35 saccharide to another.

5 Preparation

 The albuterol containing formulation according to the invention is prepared, for example, by dry blending the components, e.g., a heteropolysaccharide, a homopolysaccharide, an inert filler, and a hydrophobic material, followed by the addition of a suitable amount of water, with continued blending, followed by dry granulation in a fluid bed dryer and then milling of the resulting granulation product. Albuterol sulfate, in an amount ranging from, e.g., about 2 through about 50% by weight of the total formulation, or preferably from about 1 through about 10% by weight or more preferably from about 1 through about 6% by weight of the total formulation, is then compounded with the granulation product and formed into pills, caplets or capsules. Whatever the formulation, it is preferred that such pills, caplets or capsules each contain an effective therapeutic amount of albuterol or a derivative or salt thereof. Simply by way of example, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 4 to about 16 mg of albuterol free base per dosage unit of the free base. More preferably, the pills, caplets or capsules can contain an amount of albuterol sulfate equivalent to about 8 to about 12 mg of the free base. Simply by way of comparison, 9.6 mg of albuterol sulfate is equivalent to 8 mg of free base. Effective amounts of other pharmaceutically acceptable albuterol derivatives or salts thereof may be used, with the amounts adjusted in proportion to the weight ranges provided for albuterol free base.

5 Dissolution Testing

 The test formulations were evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests were performed using a USP Type III (VanKel Bio-Dis II) apparatus. Effects of pH, agitation, polarity, enzymes and bile salts were evaluated.

15 Bioavailability Study

 A study was conducted to evaluate the bioavailability of a test formulation of albuterol sulfate using a randomized, balanced, open label, single dose, crossover design. The study was performed using 12 healthy male and female volunteers between the ages of 18 and 35. Blood samples were removed at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 15 and 25 hours. Except for the "fed" treatment in which the subjects received a standard high fat breakfast, no food was allowed until a standard lunch was served four hours after the dose was administered. The data from each time point were used to derive pharmacokinetic parameters: area under plasma concentration-time curve ("AUC") such as AUC_{0-t}, AUC_{0-∞}, mean peak plasma concentration ("C_{max}") and time to mean peak plasma concentration ("T_{max}") which data confirmed that the formulation according to the invention provided controlled release of albuterol sulfate.

 The invention is further described in the following examples, based upon the above described methods, which are in no way intended to limit the scope of the invention.

5

EXAMPLES 1-2Preparation of Controlled Release Formulations with
Carboxymethylcellulose and Dissolution Tests Thereon

10

15

20

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients used for Examples 1-2 are set forth in Table 1 below:

TABLE 1

25

The hydrophobic polymer is carboxymethylcellulose ("CMC").

30

Component	Example 1	Example 2
1. Xanthan gum	10%	10%
2. Locust bean gum	10	10
3. CMC	10	30
4. Dextrose	70	50
5. Water	23*	23*

35

* Removed during processing.

40

Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of medicament (in the following examples the medicament is albuterol sulfate), in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF, commercially available from the

30

5 Edward Mendell Co., Inc.) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 2.9% (Ex. 1) or 4.7% (Ex. 2) by weight, respectively, of albuterol sulfate. The tablets produced by Examples 1 and 2 weighed 334.6 mg and 204.7 mg, respectively. The proportions of the tablets of Examples 1 and 2 are set forth in Table 2 below.

TABLE 2

15	Component	Example 1	Example 2
	1. SRE*	95.6%	93.8%
	2. Albuterol sulfate	2.9	4.7
	3. Sodium stearyl fumarate	1.5	1.5

20 *Sustained release excipient.

Dissolution tests were then carried out on the tablets of Examples 1 and 2. The dissolution tests were conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours.

TABLE 3

	Time (hrs)	Example 1	Example 2
30	0 (% release)	0.0	0.0
	2	28.2	30.7
	4	41.5	49.5
	6	54.5	67.2
	8	64.3	79.8
35	10	71.0	91.2
	12	78.7	96.5
<hr/>			
	Tablet wt(mg)	334.6	204.7
	Diameter (in)	3/8	3/8
40	Hardness (Kp)	6.5	2.6

5 The tablet of Example 1, with a higher percentage of sustained release excipient, provided the most prolonged release in the dissolution test.

10 EXAMPLES 3-4
Preparation of Controlled Release
Formulations with Cellulose Acetate
Phthalate and Dissolution Tests Thereon

15 The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent as described for Examples 1-2, *supra*, but with cellulose acetate phthalate ("CAP") as the hydrophobic polymer, as
20 detailed by Table 4, below, for Examples 3 and 4.

TABLE 4

Component	Example 3	Example 4
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. CAP	10	30
4. Dextrose	60	40
5. Water	10*	17*

30 * Removed during processing.

35 Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1-2, *supra*. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 3 and 4 weighed 334.6 mg. The proportions of the tablets of Examples 3 and 4 are set forth in Table 5 below:

5

TABLE 5

Component	Example 3	Examples 4
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

10

*Sustained release excipient.

15

20

Dissolution tests were then carried out on the tablets of Examples 3 and 4. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 through 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 6 below.

25

TABLE 6

30

35

Time (hrs)	Example 3	Example 4
0 (% release)	0.0	0.0
1	36.0	36.2
2	50.2	49.4
4	65.1	61.4
6	73.5	70.7
8	83.1	77.0
10	86.3	81.6
12	91.0	86.1
Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	5.8	5.8

40

The tablet tested in Example 4 provided the most

5 prolonged release in the dissolution test.

EXAMPLES 5-6

Preparation of Controlled Release Formulations with
Polyvinyl Acetate Phthalate and Dissolution Tests
Thereon

10

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable
15 hydrophobic polymer and an inert diluent as described for Examples 1-2, *supra*, but with polyvinyl acetate phthalate ("PVAP") as the hydrophobic polymer, as detailed by Table 7, below, for Examples 5 and 6.

20

TABLE 7

<u>Component</u>	<u>Example 5</u>	<u>Example 6</u>
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. PVAP	10	30
25 4. Dextrose	60	40
5. Water	18*	23*

* Removed during processing.

30

Next, the sustained release excipient prepared as detailed above was dry blended with a desired amount of albuterol sulfate, as described for Examples 1-2, *supra*. This final mixture was then compressed into tablets, each tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 5
35 and 6 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 5 and 6 are set forth in Table 8 below:

5

TABLE 8

Component	Example 5	Example 6
1. SRE*	95.6%	95.6%
2. Albuterol sulfate	2.9	2.9
3. Sodium stearyl fumarate	1.5	1.5

10

*Sustained release excipient.

15

Dissolution tests were then carried out on the tablets of Examples 5 and 6. The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, in the stomach (acid buffer with a pH of 1.5 for time: 0 through 1 hour) and in the intestines (alkaline buffer with a pH of 7.5 for time: 1 through 12 hours) (Paddle Type II, 50 rpm in 500 mL.) The results are set forth as percent release as a function of time, in hours, in Table 9 below.

20

TABLE 9

Time (hrs)	Example 5	Example 6
0 (% release)	0.0	0.0
1	36.4	36.5
2	51.3	47.4
4	66.2	57.6
6	71.8	66.0
8	79.9	70.4
10	84.2	77.2
12	86.4	77.7

30

35

Tablet wt(mg)	334.6	334.6
Diameter (in)	3/8	3/8
Hardness (Kp)	5.9	8.6

40

The tablet tested in Example 6 provided the most prolonged release in the dissolution test.

5

EXAMPLES 7-8

Preparation of Controlled Release Formulations
with Hydroxypropylmethylcellulose
10 Phthalate and Dissolution Tests Thereon

The sustained release excipient was prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable
15 hydrophobic polymer and an inert diluent as described for Examples 1-2, *supra*, but with hydroxypropylmethylcellulose phthalate ("HPMCP") as the hydrophobic polymer, as detailed by Table 10, below, for Examples 7 and 8.

20

TABLE 10

Component	Example 7	Example 8
1. Xanthan gum	15%	15%
2. Locust bean gum	15	15
3. HPMCP	10	30
25 4. Dextrose	60	40
5. Water	13*	18*

* Removed during processing.

30

As for the previous examples, the sustained release excipient was prepared as detailed above and then dry blended with a desired amount of albuterol sulfate, as described for Examples 1-2, *supra*. This final mixture was then compressed into tablets, each
35 tablet containing 2.9% by weight of albuterol sulfate. The tablets produced by Examples 7 and 8 weighed 334.6 mg, respectively. The proportions of the tablets of Examples 7 and 8 are set forth in Table 11 below:

40

TABLE 11

Component	Example 7	Example 8
-----------	-----------	-----------

36

- 5 1. SRE* 95.6% 95.6%
 2. Albuterol sulfate 2.9 2.9
 3. Sodium stearyl fumarate 1.5 1.5

*Sustained release excipient.

10

The dissolution tests were conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract, as described supra for, e.g., Examples 5-6. The results are set forth as percent release as a function of time, in hours, in Table 12 below.

15

TABLE 12

	Time (hrs)	Example 7	Example 8
20	0 (% release)	0.0	0.0
	1	33.7	32.7
	2	48.2	42.8
	4	63.9	60.3
	6	74.8	71.2
25	8	79.6	74.6
	10	85.6	82.3
	12	87.0	87.2
<hr/>			
	Tablet wt(mg)	334.6	334.6
30	Diameter (in)	3/8	3/8
	Hardness (Kp)	6.5	8.3

The data of Table 12 indicates that both Examples 7 and 8 provided effective prolongation of albuterol release in the dissolution test.

35

EXAMPLES 9-12

40

Preparation of Controlled Release Formulations
with Ethylcellulose Coating and Dissolution Tests
Thereon

5 The sustained release excipient was prepared by
dry blending the requisite amounts of xanthan gum,
locust bean gum and an inert diluent as described for
Examples 1-2, *supra*, but with no hydrophobic polymer,
10 and with an extra 2 minutes of granulation after the
addition of the components (for 4 total minutes of
post-addition granulation). Ethylcellulose aqueous
dispersion was substituted for water in the above
methods. The components of the excipient for Examples
15 9-12 are detailed by Table 13, below.

TABLE 13

	<u>Component</u>	<u>Excipient for Examples 9-12</u>
20	1. Xanthan gum	12%
	2. Locust bean gum	18
	3. Dextrose	65
	4. EAD*	5*
25	* EAD is an ethylcellulose aqueous dispersion containing approximately 25% by weight of solids. The amount added to the formulation (i.e., 5%) is solids only. Available commercially as, e.g., Surelease®, from Colorcon.	

30 The xanthan gum and locust bean gum was dry
blended in a V-blender for 10 minutes, the dextrose was
added and the mixture blended for another 5 minutes.
The EAD was then added, followed by an additional 5
35 minutes of blending. The resulting granulation was
then compressed into tablets with sodium stearyl
fumarate, as a tableting lubricant. The tablets were
then coated with additional ethylcellulose aqueous

5 dispersion. To accomplish this, ethylcellulose
(Surelease®, 400 g) was mixed with water (100 g) to
form an aqueous suspension. Thereafter, the tablets
were coated in a Keith Machinery coating pan (diameter
350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm;
10 tablets bed temperature 40°-50°C; charge per batch 1 kg;
dry air - Conair Prostyle 1250, 60°-70°C). The tablets
were coated to a weight gain of about 5%.

The tablets weighed 181.4 mg, respectively. The
proportions of the tablets are set forth in Table 14
15 below:

TABLE 14

20	<u>Component</u>	<u>Percent</u>
	1. SRE*	8.2%
	2. Albuterol sulfate	5.3
	3. Polyvinyl acetate phthalate	5.0
25	4. Sodium stearyl fumarate	1.5
	*Sustained release excipient.	

The dissolution tests were conducted in an auto-
mated USP dissolution apparatus in such a way as to
model passage through the gastrointestinal tract, as
described *supra* for, e.g., Examples 5-6. The results
30 are set forth as percent release as a function of time,
in hours, in Table 15, below. The columns are
identified as "Uncoated" (Ex. 9) 2% (Ex. 10), 3% (Ex.
11) and 4% (Ex. 12) coating by weight.

TABLE 15

	Ex. 9	Ex. 10	Ex. 11	Ex. 12
<u>Time (hrs)</u>	<u>Uncoated</u>	<u>2%</u>	<u>3%</u>	<u>4% (coat %</u>
<u>w/w)</u>				
0 (% release)	0.0	0.0	0.0	0.0
1	41.7	11.2	0.0	0.0
2	56.7	21.9	2.3	0.0
4	73.0	41.2	16.2	4.6
6	82.5	60.3	37.1	21.3
8	87.9	74.9	54.5	40.3
10	91.0	82.5	65.2	54.0
12	93.9	88.5	84.1	67.5

Tablet wt (mg)	181.4
Diameter (in)	3/8
Hardness (Kp)	7.9

The above table clearly indicates that a prolongation of release is obtained that is proportional to the percent of hydrophobic coating, by weight.

In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of coated tablets as tested above in Examples 9-12, the same tablets were tested, in vitro, for dissolution rates in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH - time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 16, below.

TABLE 16
Fed/Fast Dissolution Protocol

	"Fasted"	"Fed"
Apparatus:	Type III	Type III
Media:	0 - 1 hr pH 1.5	30% peanut oil
	1 - 2 hr pH 3.5	
	2 - 4 hr pH 5.5	

5

Agitation: 4 - 12 hr pH 7.5
15 cpm
Volume: 250 mL

15 cpm
250 mL

10

TABLE 17
Fed/Fast Dissolution Results

	<u>Time (hrs)</u>	<u>"Fasted"</u> Uncoated	<u>"Fasted"</u> 2%	<u>"Fed"</u> Uncoated	<u>"Fed"</u> 2%
	0 (% release)	0.0	0.0	0.0	0.0
15	1	48.8	15.5	28.8	18.4
	2	68.5	28.8	49.8	39.9
	4	87.2	49.5	91.9	78.9
	6	96.1	65.9	100.0	97.3
	8	100.0	80.7	100.0	100.0
20	12	100.0	100.0	100.0	100.0

As can be appreciated from table 17, the dissolution rates (in vitro) in the presence of 30% peanut oil ("Fed") are not significantly different from the dissolution rates in the absence of the 30% peanut oil ("Fast"), thus demonstrating both the improved control of release rate provided by the 2% ethylcellulose coating and the freedom from significant "Fed/Fast" effects provided by the formulations of the present invention.

5

RESULTS AND DISCUSSION

Figures 1 and 2 show in vitro dissolution profiles for the product formulated according to Table 14 and Table 15 (Example 10) i.e., the formulation of Table 14 with a 2% ethylcellulose coating. The mean in vivo plasma profile for the test product is provided in Figure 3. Figure 1 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10) as described above. The dissolution profile of Figure 1 was conducted as a Type II dissolution with a pH change to simulate gastric and enteric passage and stirring at 50 rpm (acid buffer with a pH of 1.5 for time: 0 through 1 hour followed by alkaline buffer with a pH of 7.5 for time: 1 through 12 hours). Figure 2 shows a dissolution profile of an albuterol containing tablet formulated according to Table 14 and Table 15 as described above and conducted as a Type III dissolution with a pH change to simulate gastric and enteric passage (pH profile as described by Table 16 above) and stirring at 15 rpm. Figure 3 shows an albuterol plasma profile of provided by ingestion of an albuterol containing tablet formulated according to Table 14 and Table 15 (Example 10): solid circles mark curve of plasma profile in fed subject; open circles mark curve of plasma profile in fasted subjects.

Analysis of the pharmacokinetic parameters C_{max} , T_{max} , and AUC_{∞} (Table 18) confirms that the tested formulation is an ideal candidate for a 12 hour albuterol formulation. Furthermore, a comparison of the test product in the fed and fasted states show that

35

the test product is not significantly affected by food. A delay of gastric emptying, which is expected in the fed state, accounts for the extended time required to reach the maximum plasma concentration.

Table 18: Albuterol Pharmacokinetics

Parameter		TIMERx fasted	TIMERx fed
C _{max}	mean	10.5	10.6
	%CV	39.0	31.0
T _{max}	mean	4.5	7.0
	%CV	29.0	23.0
AUC _{Inf}	mean	113.4	128.1
	%CV	30.0	20.0

Ratios	C _{max}	T _{ma}	AUC Inf
TIMERx fasted: TIMERx fed	0.98	0.64	0.89
TIMERx fed: TIMERx fasted	1.02	1.57	1.13

Confidence Limits	C _{max} LL	C _{max} UL	AUC _{Inf} LL	AUC _{Inf} UL
TIMERx fed vs TIMERx fasted	89	124	102	133

Table 19

Parameter	TIMERx-fasted	TIMERx-fed
AUC _∞	57.3-156.2	75.6-161.1
C _{max}	4.6-18.4	6.0-15.9
T _{max}	3.0-6.0	3.0-8.0
Parameter	TIMERx-fed	
AUC _∞	89.9-149.2	
C _{max}	7.0-11.9	
T _{max}	3.0-10.0	

CONCLUSION

From the results provided in above examples, it can be seen that the formulations according to the invention provide a controlled release of an active medicament such as albuterol sulfate without any significant differences induced by a "fed/fast" effect due to the presence of food in the gastrointestinal tract. Accordingly, the results provide that the tablets produced according to the invention are suitable for delivering medicaments as an oral solid dosage form over a 24-hour oral period of time.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims. Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

5 What is claimed is:

1. A controlled release solid dosage form for oral administration of a therapeutically active medicament to a patient in need thereof, comprising:

10 a pharmaceutically effective amount of a medicament to be administered to a patient in need of said medicament;

15 a sustained release excipient comprising a gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of reciprocally cross-linking when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum being from about 1:3 to about 3:1; an inert pharmaceutical diluent selected from the group consisting of a pharmaceutically acceptable
20 saccharide, polyhydric alcohol, a pre-manufactured direct compression diluent, and mixtures of any of the foregoing, the ratio of said inert diluent to said gelling agent being from about 1:8 to about 8:1, said dosage form providing a sustained release of said
25 medicament when exposed to an environmental fluid and a pharmaceutically acceptable hydrophobic material.

30 2. The controlled release solid dosage form according claim 2 wherein said diluent is a saccharide selected from the group consisting of sucrose, dextrose, lactose, microcrystalline cellulose, fructose, xylitol, sorbitol, a starch, and mixtures thereof.

35

5 3. The controlled release solid dosage form
 according claim 1, wherein said heteropolysaccharide
 gum comprises xanthan gum and said homopolysaccharide
 gum comprises locust bean gum.

10 4. The controlled release solid dosage form
 according claim 2, wherein said xanthan gum and said
 locust bean gum are present in about a 1:1 ratio,
 respectively, by weight.

15 5. The controlled release solid dosage form
 according to claim 1, wherein said hydrophobic material
 is selected from the group consisting of a cellulose
 ether, a cellulose ester and an alkylcellulose.

20 6. The controlled release solid dosage form
 according claim 1, wherein said hydrophobic material is
 selected from the group consisting of ethylcellulose,
 carboxymethylcellulose, cellulose acetate phthalate,
 hydroxypropylmethylcellulose phthalate and a polyvinyl
25 acetate polymer.

 7. The controlled release solid dosage form
 according claim 1, wherein said hydrophobic material is
 present in an amount ranging from about 1 through about
30 90%, by weight, of the solid dosage form.

 8. The controlled release solid dosage form
 according claim 1, wherein said hydrophobic material is
 present in an amount ranging from about 25% through
35 about 50%, by weight, of the solid dosage form.

5 9. The controlled release solid dosage form according to claim 1 wherein said medicament is a pharmaceutically effective amount of albuterol or a salt or derivative thereof.

10 10. The controlled release solid dosage form according to claim 1 which is a tablet.

 11. The controlled release solid dosage form according to claim 1 which is in granular form.

15 12. The controlled release solid dosage form according to claim 11, which comprises a gelatin capsule containing a sufficient amount of said granules to provide an effective dose of said therapeutically active medicament.

 13. The controlled release solid dosage form according to claim 9, wherein said hydrophobic material is selected from the group consisting of

25 carboxymethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, ethylcellulose, a copolymer of acrylic and methacrylic and esters, waxes, shellac, zein, and mixtures of any of the fore-

30 going, prior to incorporation of said medicament, said hydrophobic material being included in said dosage form in an amount effective to slow the hydration of said gelling agent when exposed to an environmental fluid.

35 14. The controlled release solid dosage form according to claim 12 which is a tablet, at least part of a surface of said tablet being coated with a

5 hydrophobic material to a weight gain from about 1 to
about 20 percent, by weight.

15. The controlled release solid dosage form
according to claim 1 which comprises a granulation
10 which is coated with a hydrophobic material to a weight
gain from about 1% to about 20%.

16. The controlled release solid dosage form
according to claim 14, wherein said hydrophobic
15 material is selected from the group consisting of a
cellulose ether, a cellulose ester and an
alkylcellulose.

17. The controlled release solid dosage form
20 according to claim 16 which is a tablet, at least part
of a surface of said tablet being coated with a
hydrophobic material to a weight gain from about 1 to
about 20 percent, by weight.

18. The controlled release solid dosage form
25 according to claim 17, wherein said mixture of
sustained release excipient and medicament are coated
with a hydrophobic material prior to tableting.

19. The controlled release solid dosage form
30 according to claim 1 which is a tablet, said tablet
further comprising a coating containing from about 10
to about 40 percent of the total amount of said
medicament included in said dosage form.

5 20. The controlled release solid dosage form according to claim 1 wherein the amount of albuterol is an amount equivalent to about 4 mg to about 16 mg of albuterol free base.

10 21. A method of preparing a controlled release solid dosage form comprising a medicament for oral administration, the method comprising
 preparing a sustained release excipient comprising from about 10 to about 99 percent by weight of a
15 gelling agent comprising a heteropolysaccharide gum and a homopolysaccharide gum capable of cross-linking said heteropolysaccharide gum when exposed to an environmental fluid, the ratio of said heteropolysaccharide gum to said homopolysaccharide gum
20 being from about 1:3 to about 3:1, and from about 0 to about 89 percent by weight of an inert pharmaceutical diluent, and from about 1 to 90% by weight of a pharmaceutically acceptable hydrophobic material; and
 adding an effective amount of a medicament
25 thereto, such that a final product is obtained having a ratio of said medicament to said gelling agent from about 1:3 to about 1:8, such that a gel matrix is created when said formulation is exposed to environmental fluid and said formulation provides
30 therapeutically effective blood levels of said medicament for at least 12 hours.

 22. The method of claim 21, further comprising
35 tableting said mixture of said sustained release excipient and said medicament.

5 23. The method of claim 21, further comprising
coating said tablets with a hydrophobic coating to a
weight gain from about 1% to about 20%.

10 24. The method of claim 21, further comprising
granulating said sustained release excipient with a
hydrophobic material.

15 25. The method of claim 21, wherein said
medicament is albuterol or a salt or derivative
thereof.

 26. The method of claim 21, wherein said
hydrophobic coating comprises ethylcellulose.

20 27. The method of claim 25, wherein the amount of
albuterol is an amount equivalent to about 4 mg to
about 16 mg of albuterol free base.

25 28. The method of claim 21, wherein said
sustained release excipient comprises from about 10 to
about 75 percent gelling agent, from about 0 to about
90% hydrophobic material and from about 30 to about 75
percent inert diluent.

30 29. The method of claim 21, wherein said
formulation provides therapeutically effective blood
levels of said medicament for at least 24 hours.

35 30. The method of claim 21, further comprising
compressing the mixture of said sustained release
excipient and said tablet into tablets.

5 31. The method of claim 21, wherein said
medicament comprises a therapeutically effective dose
of albuterol or salts and derivatives of the same.

10 32. A method of treating a patient with albuterol
comprising,

 preparing a sustained release excipient comprising
from about 10 to about 99 percent by weight of a
gelling agent comprising a heteropolysaccharide gum and
a homopolysaccharide gum capable of cross-linking said
15 heteropolysaccharide gum when exposed to an
environmental fluid, the ratio of said
heteropolysaccharide gum to said homopolysaccharide gum
being from about 1:3 to about 3:1, and from about 0 to
about 89 percent by weight of an inert pharmaceutical
20 diluent, and from about 1 to 90% by weight of a
pharmaceutically acceptable hydrophobic material; and
 adding an effective amount of a albuterol, or a
salt or derivative thereof, to said sustained release
excipient, such that a final product is obtained having
25 a ratio of albuterol to said gelling agent from about
1:3 to about 1:8, such that a gel matrix is created
when said formulation is exposed to environmental fluid
and said formulation provides therapeutically effective
blood levels of albuterol for at least 12 hours.

30 adding an amount of albuterol effective to render
a desired therapeutic effect;

 tableting the resultant mixture such that a final
product is obtained having a ratio of albuterol to said
gelling agent from about 1:3 to about 1:8, such that a
35 gel matrix is created when said tablet is exposed to
gastrointestinal fluid and said tablet provides
therapeutically effective blood levels of albuterol;

5 and

 administering said tablet to a patient at a
predetermined dosage interval from about 12 to about 24
hours.

10 33. The method of claim 32, further comprising
coating said tablets with a hydrophobic material to a
weight gain from about 1% to about 20%.

15 34. The method of claim 32, further comprising
preparing said formulation such that it provides
therapeutically effective blood levels of said
medicament for at least 24 hours.

20 35. The controlled release solid dosage form of
claim 1 which, when orally administered to a patient,
provides a medicament plasma concentration-time curve
with an area under the curve, to infinity, ranging from
about 89 to about 150 (ng-hours/ml).

25 36. The controlled release solid dosage form of
claim 1 which, when orally administered to a fasting
patient, provides a medicament plasma concentration-
time curve with an area under the curve, to infinity,
ranging from about 57 to about 157 (ng-hours/ml).

30 37. The controlled release solid dosage form of
claim 1 which, when orally administered to a fed
patient, provides a medicament plasma concentration-
time curve with an area under the curve, to infinity,
35 ranging from about 75 to about 162 (ng-hours/ml).

5 38. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a mean peak plasma concentration ranging from about 7 to about 12 ng/ml.

10 39. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a mean peak plasma concentration ranging from about 4.5 to about 19 ng/ml.

15 40. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a mean peak plasma concentration ranging from about 6 to about 16 ng/ml.

20 41. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a time to mean peak plasma concentration ranging from about 3 to about 10 hours.

25 42. The controlled release solid dosage form of claim 1 which, when orally administered to a fasting patient, provides a time to mean peak plasma concentration ranging from about 3 to about 6 hours.

30 43. The controlled release solid dosage form of claim 1 which, when orally administered to a fed patient, provides a time to mean peak plasma concentration ranging from about 3 to about 8 hours.

5 44. The controlled release solid dosage form of claim 35 wherein the area under the plasma concentration curve, to infinity, ranges from about 112 to about 129 (ng-hours/ml).

10 45. The controlled release solid dosage form of claim 38 wherein the mean peak plasma concentration ranges from about, 9.5 to about 12 ng.

15 46. The controlled release solid dosage form of claim 42 wherein the time to mean peak plasma concentration ranges from about 3.5 to about 8 hours.

20 47. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve wherein time to peak plasma concentration in a fasted patient divided by a time to peak plasma concentration in a fed patient ranges from about 0.50 to about 0.70.

25 48. The controlled release solid dosage form of claim 1 which, when orally administered to a patient, provides a medicament plasma concentration-time curve wherein peak plasma concentration in a fasted patient divided by peak plasma concentration in a fed patient
30 ranges from about 0.90 to about 1.10.

1/3

FIGURE 1
Albuterol Dissolution Profile

Type II - pH 4 Method - 50 rpm

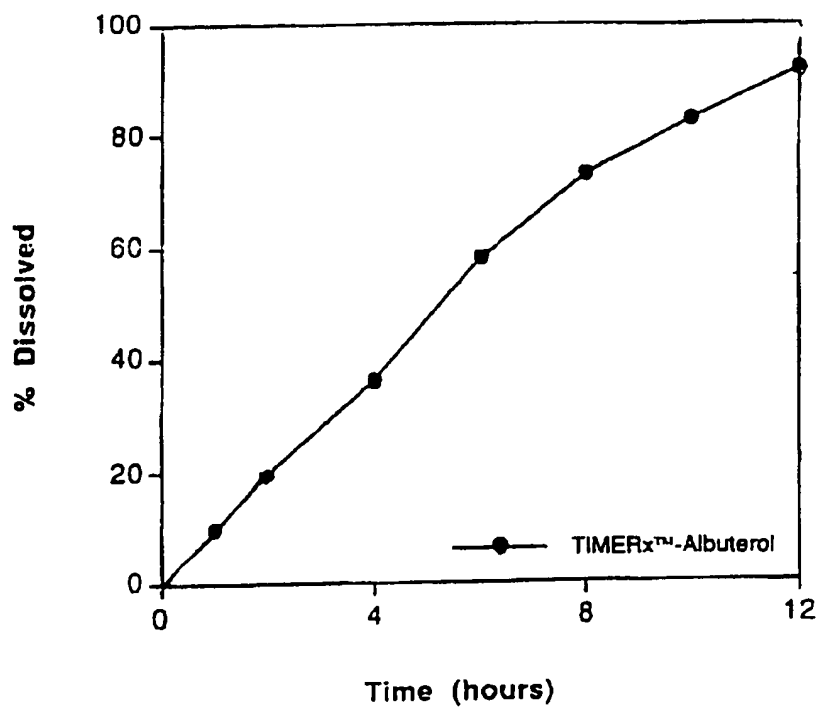


FIGURE 2
Albuterol Dissolution Profile
Type III - pHΔ Method - 15 cpm

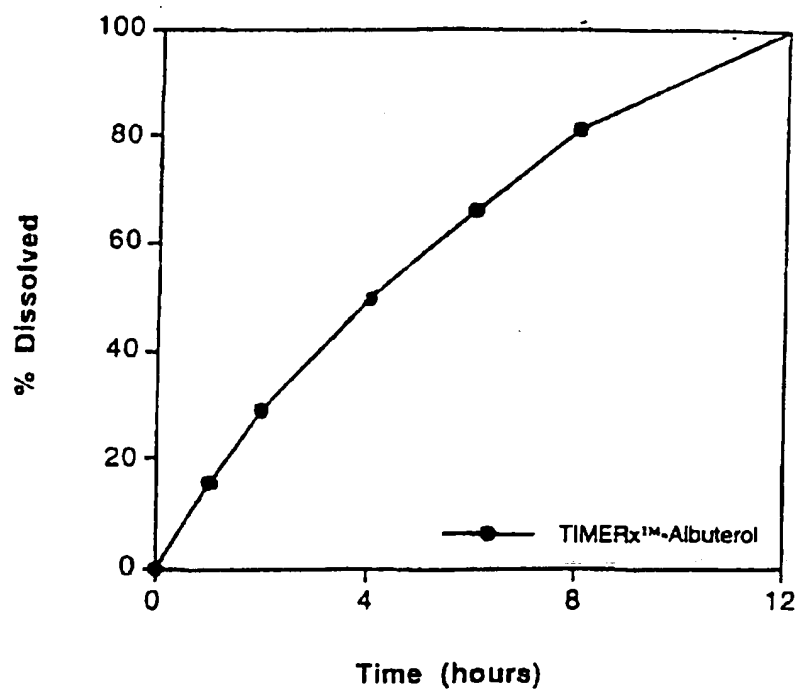
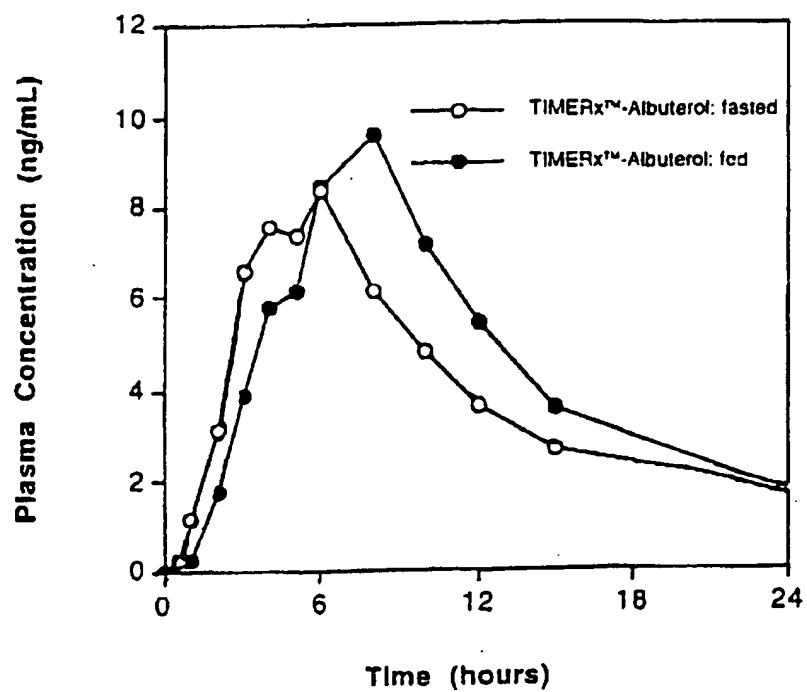


FIGURE 3
Albuterol Plasma Profile



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/17991

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/14, 9/22

US CL :424/457, 468, 488; 514/777, 778, 779, 780, 781, 964, 965

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/457, 468, 488; 514/777, 778, 779, 780, 781, 964, 965

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,455,046 (BAICHWAL) 03 October 1995, see claims 1-51.	1-48

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

24 JANUARY 1997

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05 MAR 1997

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Box PCT
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Facsimile No. (703) 305-3230

Authorized officer

NATHAN M. NUTTER scc

Telephone No. (703) 308-1235

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